33 Koo OM, Rao AV. Long-term effect of bifidobacteria and Neosugar on precursor lesions of colonic cancer in CF1 mice. Nutr Rev 1991;51:137-146.
34 Reddy BS, Rivenson A. Inhibitory effect of Bifidobacterium longum on colon, mammary, and liver carcinogenesis induced by 2-amino-3-methylimidazo [[4,5-f]] quinoline, a food mutagen. Cancer Res 1993;53:3914-3918.
35 Buddington RK, Williams CH, Chen S-C, Witherly SA. Dietary supplement of Neosugar alters the fecal flora and decreases activities of some reductive enzymes in human subjects. Am J Clin Nutr 1996;63:709-716.
36 Famularo G, Moretti S, Marcellini S, De Simone C. Stimulation of immunity by probiotics. In: Fuller R, editor. Probiotics: therapeutic and other beneficial effects. London: Chapman and Hall, 1997. p. 133-161.
37 Schiffrin EJ, Brassart D, Servin AL, et al. Immune modulation of blood leukocytes in humans by lactic acid bacteria: criteria for strain selection. Am J Clin Nutr 1997;66(suppl):15S-20S.
38 Standiford TK, Arenberg DA, Danforth JM, et al. Lipoteichoic acid induces secretion of interleukin-8 from human blood monocytes: a cellular and molecular analysis. Infect Immun 1994;62:119-125.
39 Op den Camp HJM, Oosterhof A, Veerkamp JH. Interaction of bifidobacterial lipoteichoic acid with human intestinal epithelial cells. Infect Immun 1984;47:332-334.
40 Kleeman EG, Klaenhammet TR. Adherence of Lactobacillus species to human fetal intestinal cells. J Dairy Sci 1982;65:2063-2069.
41 Perdigon G, de Macios ME, Alvarez S, et al. Effect of perorally administered lactobacilli on macrophage activation in mice. Infect Immun 1986;53:404-410.
42 Matsumara K, Kitazawa H, Itoh T, Yamaguchi T. Interferon induction by murine peritoneal macrophage stimulated with Lactobacillus gasseri. Animal Sci Technol (Jpn) 1992;63:1157-1159.
43 Solis Pereyra B, Lemmonier D. Induction of human cytokines to bacteria used in dairy foods. Nutr Res 1993;13:1127-1140.
44 Yasui H, Ohwaki M. Enhancement of immune response in Peyer's patch cells cultured with Bifidobacterium breve. J Dairy Sci 1991; 74:1187-1195.
45 Yasui H, Nagaoka N, Mike A, et al. Detection of bifidobacterium strains that induce large quantities of IgA. Microb Ecol Health Dis 1992;5:155-162.
46 De Simone C, Ciardi A, Grassi A, et al. Effect of Bifidobacterium bifidum and Lactobacillus acidophilus on gut mucosa and peripheral blood B lymphocytes. Immunopharmacol Immunotoxicol 1992;14:331-340.
47 Majamaa H, Isolaurie E. Probiotics: a novel approach in the management of food allergy. J Allergy Clin Immunol 1997;99:179-185.
48 Hopkins MJ, Cummings JH, Macfarlane GT. Interspecies differences in maximum specific growth rates and cell yields of bifidobacteria cultured on oligosaccharides and other simple carbon sources. J Appl Microbiol 1998;85:381-386.

Complementary and alternative medicine in cardiovascular disease: what is the evidence it works?

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Despite advances in prevention and treatment over the past 20 years, cardiovascular disease remains a leading cause of death and disability. This article reviews coenzyme Q10, hawthorn, complementary chelation, and ginkgo biloba, some of the most common treatments patients ask about and use for cardiovascular diseases.

Summary points

- Coenzyme Q10 and hawthorn merit further investigation to determine what benefits, if any, they offer beyond best present therapies for cardiac ischemia and heart failure.
- The few studies of best design do not support the use of chelation therapy for cardiovascular disease.
- Ginkgo biloba is at least as effective as pentoxifylline for treatment of claudication, and further investigation, perhaps in combination with exercise, is warranted.
- Dietary supplements manufactured in the United States are of inconsistent purity and potency, making it difficult for physicians to advise their patients about how to purchase and use them.

Methods

For Coenzyme Q10 and hawthorn, MEDLINE, BIOSIS and Cochrane databases were reviewed along with references of retrieved articles and personal files of the author. Languages were restricted to English and German. Articles discussed reflect often cited references, not an exhaustive review. The discussion of chelation therapy summarizes a review of studies identified using MEDLINE (1966–1996) and CISCOM (1996) bibliographies of relevant papers and suggestions from six experts and national societies. For the *Ginkgo biloba* for peripheral vascular disease, literature searches located eight randomized placebo-controlled double-blind trials that met inclusion criteria.

Coenzyme Q10

Coenzyme Q10 is used widely in Japan, Europe, and elsewhere for a variety of purposes, but especially for cardiac disease. It is a fat-soluble, vitamin-like substance, structurally similar to vitamins E and K. It is one of many agents called ubiquinones, so named because of their presence in almost all cells of the human body. Its endogenous forms serve as essential cofactors and participate in ATP production within the mitochondria, oxidative phosphorylation, and antioxidation in membranes.[1]

Coenzyme Q10 is undergoing investigation as a treatment for diverse disorders such as Parkinson's disease and mitochondrial myopathies and for its effects on lipoprotein (a).[2-4] One of its most common uses, however, is as adjunctive therapy in the treatment of cardiovascular disease, where it has been studied for improvement of left ventricular pump function and reduction of the signs and symptoms of ischemia. A recent MEDLINE search (July 1999) for the term

"coenzyme Q10" revealed 780 articles, yet only recently has investigation focused on clinical outcomes.

In 1985 a randomized double-blind placebo-controlled crossover trial of 12 patients with stable angina pectoris used multistage treadmill exercise tests to evaluate the frequency of angina, nitroglycerin consumption, and exercise time to defined ST-segment depression.[5] Both the time until ST-segment depression and total exercise time increased significantly with coenzyme Q10, whereas there were trends to a fall in the frequency of angina at rest and nitroglycerin consumption in the treated group compared to controls. No comparison of the postrandomized groups was offered.

Nitroglycerin was the only cardioactive medication allowed. Two points that could lead to underestimation of treatment were the small number of patients and the relatively small dose of coenzyme Q10 (50 mg tid). Also of concern was the lack of a washout period between treatment and placebo. Lastly, increased serum coenzyme Q10 levels related significantly to the increased exercise duration; and ST-segment depression, heart rate, and pressure-rate product showed no differences at the same and maximal workloads. No patients dropped out; one treated patient reported loss of appetite. The authors suggest that coenzyme Q10 may be a safe and promising treatment for angina pectoris.

Chello et al. studied the effects of oral coenzyme Q10 taken perioperatively on reperfusion injury associated with coronary artery bypass grafting.[6] They randomly divided 40 patients undergoing elective surgery to a coenzyme Q10 group (150 mg/day) or control group, presumably receiving routine care only. The study was not completely blinded. They sampled arterial and coronary sinus concentrations of creatine kinase and other indicators of ischemia at several intervals perioperatively. They also observed incidence of postoperative ventricular arrhythmias and dopamine requirements. The authors report significantly lower enzyme levels in the treated group, along with significantly fewer arrhythmias and lower doses of dopamine required for inotropic support.

The authors conclude that coenzyme Q10 pretreatment inhibits perioperative lipid peroxidation, possibly decreasing sensitivity of the sarcolemma to ischemic challenge and reducing complications as noted.

A 1993 study by Morisco et al. randomized 641 patients with New York Heart Association (NYHA) functional class III and IV to receive placebo or coenzyme Q10 (2mg/kg/day) in a one-year double-blind trial.[7] They reported significantly fewer hospitalizations for worsening heart failure in the treatment group and significantly fewer episodes of pulmonary edema or "cardiac asthma." Randomization was computer generated and most patients were already taking digoxin, angiotensin converting enzyme, or diuretics.

In 1998 Singh et al. reported protective effects of coenzyme Q10 in patients with acute myocardial infarction if given within 3 days of onset of symptoms and continued for 28 days.[8] They randomized 73 patients to coenzyme Q10 (60 mg bid) and 71 patients to placebo. The authors reported a significant decrease in angina pectoris, total arrhythmias, left ventricular function, cardiac deaths, and nonfatal infarction in the treated group compared to placebo.

The study was generally well designed. No patients on entry used beta blockers, and the coenzyme Q10 group had significantly more current smokers and patients using nifedipine.

A recent study by Watson et al. evaluated quality of life (using the Minnesota "Living With Heart Failure" questionnaire), right heart pressures, cardiac output, and echocardiographic left ventricular volumes at baseline and after treatment phases of coenzyme Q10 or placebo.[9] Thirty patients with ejection fraction 26 +/– 6% were randomized to a double-blind crossover trial, with 3-month phases and 1-week washout in between phases. Notably, patients were clinically stable on the maximum tolerated doses of angiotensin-converting enzyme (ACE) inhibitor therapy; 24 were taking digoxin, 28 furosemide, and 25 hydralazine and/or nitrates. The authors found no improvement in resting left ventricular systolic function or quality of life in the coenzyme Q10 group despite a twofold elevation of serum drug levels.

The study was small but generally well designed. Patients were recruited from a heart failure and transplant unit.

Other studies have reported the benefits of coenzyme Q10 for improved inotropy, vasodilatation, exercise response, and NYHA class,[10-12] but they have often been limited by sample size, study design, or methods of measuring left ventricular response. Coenzyme Q10 has greatest bioavailability in a soybean oil preparation, and the usual oral dose varies from 100 mg to 600 mg daily in two or three divided doses. It has been well tolerated in clinical studies, with no serious side effects and infrequent reports of nausea, loss of appetite, epigastric discomfort, and diarrhea.[13] Of concern, however, are recent reports of a possible association between coenzyme Q10 and decreased responsiveness to warfarin.[14,15] Compared to other dietary supplements, coenzyme Q10 is expensive. Whether coenzyme Q10 offers benefit beyond present therapy is unknown. Clearly it should not be used in place of conventional treatments that have demonstrated effects on cardiac function and long-term outcome, but it deserves further evaluation as a safe adjunct in the management of cardiac disease.

Hawthorn

Hawthorn is commonly prescribed in Germany for New York Heart Association Class I and II patients. The flowers, leaves, bark, and red fruit all have been used for medicinal purposes. They contain oligomeric procyanidins and flavonoids[16] that may affect the heart in part by inhibition of angiotensin-converting enzymes.

Chinese herbal literature records early use of hawthorn species for a variety of medical problems, and hawthorn was observed to be of benefit for dropsy in 17th-century England. It has been recorded in numerous herbal pharmacopoeia but is notably absent from recent literature reviews.[17,18] There are few summaries of the present knowledge base regarding hawthorn.[19,20]

Schmidt et al. studied 78 patients in a randomized double-blind placebo-controlled trial of hawthorn versus placebo.[21] They evaluated the patients' working capacity by bicycle ergometry at the onset of the trial, at 28 days, and at 56 days. They also noted blood pressure, heart rate, and clinical symptoms as reported by the patients. This study was important because it used a larger dose of hawthorn (600 mg/day) than similarly designed studies with less impressive results. The randomization and blinding processes are clear and well described, and the study's few dropouts are itemized and probably of no relevance. The patients were not allowed to take ACE inhibitors, beta-blockers, calcium antagonists, long-acting nitrates, cardiac glycosides, or other cardiac medications (except long-standing diuretics) during the study.

The authors found significant improvement in maximal work capacity in the treatment group versus placebo, and work capacity continued to improve throughout the study. Clinical symptoms (fatigue, dyspnea, lack of vitality) also improved significantly and were accompanied by reduction of the systolic blood pressure (with no change in diastolic) and decrease in heart rate. The medication was well tolerated. It would be helpful to know patient beliefs about whether they were receiving treatment or placebo, and whether they participated in other exercise outside of the study.

Most of the research on hawthorn has been performed in Germany, and results from a number of randomized double-blind placebo-controlled trials of variable quality have been published. A review from 1996 summarized eight placebo-controlled trials of hawthorn for congestive heart failure (NYHA I-III).[22] All of these studies showed benefits beyond placebo and no more adverse events than placebo. It was concluded that "crataegus is an effective and safe treatment for this indication."

Whether hawthorn can offer benefit in addition to or beyond current best treatment with conventional therapy (ACE inhibitors, beta-blockers, etc.) is not known. There are no long-term outcome data to compare cardiac events, for example. Hawthorn probably has less inotropic effect than digoxin, but it also has an excellent safety record. Excessive doses are associated with hypotension and sedation.[13] Patients who choose to use hawthorn in addition to digoxin should be closely monitored to avoid overdose.

Chelation therapy

So-called "chelation therapy" for cardiovascular disease has long been a source of controversy. Numerous lay books advocate its effectiveness in treating systemic atherosclerosis, and patients often speak of it enthusiastically.[23,24] It is advocated as an alternative to revascularization procedures, available in hundreds of clinics around the country, and practiced by physicians who may belong to organizations such as the American College for Advancement in Medicine or the American Board of Chelation Therapists. Patients generally undergo one to three intravenous treatments per week for up to 40 sessions, at a total cost of $3000 to $5000.

When given intravenously, ethylene diamine tetraacetic acid is known to extract minerals from the circulation. There is no in vitro or in vivo evidence to support the contention that atherosclerosis is improved with chelation therapy through regression of calcium-laden plaques.

Numerous unblinded and uncontrolled studies have been performed, many of which claim decreased symptoms of ischemia and claudication after treatment.[25] Proper randomization, blinding, and controls are crucial, however, as many vascular disease and postmyocardial infarction patients are highly motivated to improve their diets, increase exercise, and alter stressful lifestyles, all of which may affect the course of disease. For example, in one study of chelation for peripheral vascular disease, 60% of the control group reported improvement in walking distance.[26]

A 1997 review of the few available randomized double-blind placebo-controlled trials of chelation for peripheral vascular disease did not support the results of poorly designed studies. Three trials (four papers) were analyzed. Outcomes evaluated included walking distances, ankle/arm blood pressure, angiogram results, and transcutaneous oxygen tension. The trials included 10, 153, and 30 patients, and none showed efficacy beyond placebo.[27]

Only two randomized controlled trials relating to chelation for coronary heart disease are available.[28,29] Both show no benefit in terms of objective signs or subjective improvement over and above placebo.

Chelation has been associated with causing renal problems, hypocalcemia, and death. Long-term consequences of chelation, such as possible osteoporosis, are unknown. There is presently little data and minimal theoretical basis to support randomized controlled trials.

Ginkgo biloba

In the United States, *Ginkgo biloba* is presently one of the most popular herbal remedies. It has a multitude of pharmacological effects, with a potential for alleviating circulatory problems.[30] It is licensed in Germany for the treatment of intermittent claudication. A systematic review of all randomized placebo-controlled double-blind trials on the subject summarized the evidence of eight trials that met inclusion criteria.[31] Four of them showed a significant difference in the increase of painfree walking distance in favor of ginkgo (weighted mean difference: 36.6 meters, 95% CI 28.8-43.9). Statistical pooling of the data yielded a weighted mean difference of 32.5 meters (95% CI 22.1-42.8). Adverse effects were infrequent, mild, and transient. Interestingly, this meta-analytic result compares favorably to that achieved in a recent meta-analysis for pentoxifylline.[32] *Ginkgo biloba* has platelet-inhibitory activity, and physicians should be wary of its use in patients taking anticoagulants.

Other approaches

The Dean Ornish program of lifestyle and dietary changes has been studied systematically and may help in the secondary prevention of cardiovascular disease.[33] Vitamin E is beginning to appear useful as adjunctive therapy for secondary coronary heart disease prevention, possibly for primary prevention, although the American Heart Association does not yet recommend its routine use.[34]

References

1 Greenberg S. Coenzyme 10: a new drug for cardiovascular disease. J Clin Pharmacol 1990;30(7):596-608.
2 Boschert S. Coenzyme Q10, remacemide trial underway. Internal Medicine News 1999 Mar 15;53.
3 Chan A, Reichmann H, Kogel A, et al. Metabolic changes in patients with mitochondrial myopathies and effects of coenzyme Q10 therapy. J Neurol 1998 Oct;245(10):681-685.
4 Singh R, Niaz M. Serum concentration of lipoprotein (A) decreases on treatment with hydrosoluble coenzyme Q10 in patients with coronary artery disease: discovery of a new role. Int J Cardiol 1999 Jan;68(1):23-29.
5 Kamikawa T, Kobayashi A, Yamashita T, et al. Effects of coenzyme Q10 on exercise tolerance in chronic stable angina pectoris. Am J Cardiol 1985;56:247-251.
6 Chello M, Mastroroberto P, Romano R, et al. Protection by coenzyme Q10 from myocardial reperfusion injury during coronary artery bypass grafting. Ann Thor Surg 1994;58:1427-1432.
7 Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study. Clin Investig 1993;71:S134-136.
8 Singh R, Wander G, Rastogi A, et al. Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction. Cardiovasc Drugs Ther 1998 Sep;12(4):347-353.
9 Watson P, Scalia G, Galbraith A, et al. Lack of effect of coenzyme Q on left ventricular function in patients with congestive heart failure. J Am Coll Card 1999;33(6):1549-1552.
10 Sacher H, Sacher M, Landau S, et al. The clinical and hemodynamic effects of coenzyme Q10 in congestive cardiomyopathy. Am J Ther 1997;4(2/3):66-72.
11 Morisco C, Nappi A, Argenziano L, Sarno D, et al. Non-invasive evaluation of cardiac hemodynamics during exercise in patients with chronic heart failure: effects of short-term coenzyme Q10 treatment. Mol Aspects Med 1994;15:W155-163.
12 Langsjoen P, Langsjoen P, Folkers K. Long-term efficacy and safety of coenzyme Q10 therapy for idiopathic dilated cardiomayopathy. Am J Cardiol 1990;65:521-523.
13 Burnham T, Hagemann R, Threlkeld D (editors). The review of natural products—facts and comparisons. St. Louis (MO): Wolters Kluwer. Updated monthly. August, 1977.
14 Landbo C, Almdal T. Interaction between warfarin and coenzyme Q10. Ugeskr Laeger 1998 Aug 17;160(34):4916.10.
15 Spigset O. Reduced effect of warfarin caused by ubidecarenone. Lancet 1994 Nov 12;344(8933):1372-1373.
16 Gildor A. Crataegus oxyacantha and heart failure. Circulation 1998 Jan 5;99(1):2098.
17 Howard B, Kritchevsky D. Phytochemicals and cardiovascular disease: a statement for healthcare professionals from the America Heart Association. Circulation 1997; 95:2591-2593.
18 Cleland J, Swedberg K, Poole-Wilson P. Successes and failures of current treatment of heart failure. Lancet 1998;352:19-28.
19 Crataegus oxycantha, common name: hawthorn. Altern Med Rev 1998 Apr 3;(2):138-139.
20 Gildor A. Crataegus oxyacantha and heart failure. Circulation 1998 Nov 10;98(19):2098.
21 Schmidt, U, Kuhn U, Ploch M, et al. Efficacy of the hawthorn (Crataegus) preparation LI 132 in 78 patients with chronic congestive heart failure defined as NYHA functional class II. Phytomedicine 1994;1:17-24.
22 Wiehmayr T, Ernst E. Die therapeutische Wirksamkeit von Crataegus. Fortschr Med 1996;1/2:27-29.
23 Hawken CM. Chelation therapy: an effective method for maintaining cardiovascular health. Lindon, UT: Woodland Publishing; 1998.
24 Brecher H, Brecher A. Forty something forever: a consumer's guide to chelation therapy and other heart savers. Herndon, VA: Healthsavers Press; 1993.
25 Chappell LT, Stahl JP. The correlation between EDTA chelation therapy and improvement in cardiovascular function: a meta-analysis. J Advance Med 1993;6:139-160.
26 van Rij AM, Solomon C, Packer SG, Hopkins WG. Chelation therapy for intermittent claudication. Circulation 1994;90:1194-1199.
27 Ernst E. Chelation therapy for peripheral arterial occlusive disease: a systematic review. Circulation 1997;96:1031-1033.
28 Kitchell JR, Palmon F, Ayton N, Meltzer LE. The treatment of coronary heart disease with disodium EDTA. Am J Cardiol 1963;11:501-506.
29 Hopf R, Gleußner M, Babej R, et al. Wirksamkeit von Chelat bei Patienten mit koronarer Herzkrankheit. Z. Kardiol 1997;76:Suppl 2.
30 Ernst E. Ginkgo Biloba, an herbal success story. Curr Prac Med 1998;1:53-54.
31 Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis (submitted for publication).
32 Girolami B, Bernardi E, Prins MH, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline or Natronye. Arch Int Med 1999;159:337-345.
33 Ornish D, Scherwitz L, Billings J, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998;280(23):2001-2007.
34 Tribble D. AHA Science Advisory. Antioxidant consumption and risk of coronary heart disease: emphasis on vitamin C, vitamin E, and beta-carotene: a statement for healthcare professionals from the American Heart Association. 1998.

capsule

Beware of burns from ice packs Ice packs can be just as damaging as hot water bottles if they are applied directly to the skin, warn two plastic surgeons from the UK (British Journal of Sports Medicine 1999;33:278-279). A 59 year old woman in their care sustained a partial thickness burn to the calf after a gym instructor told her to rest it on an icepack for 20 minutes. Freezing and compressing the skin at the same time is asking for trouble, they say, so always put something between the ice and the skin.